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Jeffery Flier, M.D., Ph.D.
Dean of the Faculty of Medicine
Harvard Medical School
25 Shattuck Street
Boston, Massachusetts 02115

Dear Dean Flier:

I am delighted to propose the promotion of XXXX XXX, M.D. from Associate Professor at Harvard Medical School to Professor, full-time, at Harvard Medical School. Dr. XXXX' area of excellence is Investigation. His significant supporting activity is Clinical Expertise.

DESCRIPTION OF THE CANDIDATE AND HIS/HER CONTRIBUTIONS

Background and Training

Dr. XXXX received his undergraduate degree (with honors) in Chemistry from the University of Virginia in 1983 and his medical degree from the University of Virginia School of Medicine in 1987. After a year of internship at the Albany Medical College, he came to the Massachusetts General Hospital for his residency training in Anesthesiology (1988-1991). He then completed a three-year research fellowship at the MGH under the mentorship of Professor Keith W. Miller, D.Phil., and was appointed as an Assistant Professor in Anaesthesia at HMS and an Assistant Anesthetist at the MGH in 1993. He was appointed an Associate Professor of Anaesthesia at HMS and an Associate Anesthetist at the MGH in 2001. Dr. XXXX is a Diplomate of the American Board of Anesthesiology.

Review of Current Activities

After completing his training, Dr. XXXX began his remarkably productive career, which has included outstanding achievements in translational pharmacologic research, as well as excellence in patient care, and administrative service. He currently devotes 60% of his time to laboratory research that is funded by R01, R21, and Program Project grants from the National Institutes of Health. Components of that research effort include directing laboratory

investigation on the mechanisms of anesthesia and the development of novel anesthetic agents. The excellence of his scientific investigations is evidenced by two decades of uninterrupted NIH support as a Principal Investigator, as well as the creation of sufficient promising new drugs to justify a major capital investment by Partner's Healthcare and the creation of a new pharmaceutical company, Annovation BioPharma, Inc. Dr. XXXX is the scientific founder of this company, and he spends 5 hours each month serving as the chair of its Scientific Advisory Board. Dr. XXXX also devotes a large amount of time to formal training and mentoring of undergraduate students, post-doctoral candidates, and staff physicians, as well as lecturing locally, nationally, and internationally, and reviewing grant applications and manuscripts. Despite his heavy academic burden, he is an active and highly sought-after clinician who engages in direct patient care in the operating room while teaching residents the science and art of administering anesthesia. Dr. XXXX has served as the Vice-Chairman of his department and provided an extraordinary level of administrative service to both his department and institution. Together, these research, clinical, and administrative accomplishments have earned him three *Partners in Excellence* Awards (2009, 2011, and 2012) and high recognition from his colleagues.

AREA OF EXCELLENCE: INVESTIGATION

Contributions, Achievement and Impact

Dr. XXXX is a highly productive, creative, and internationally recognized physician-scientist who rapidly became an authority in the field of anesthetic molecular mechanisms. This work originally began when Dr. XXXX was a research fellow in Dr. Keith Miller's laboratory. However upon finishing his fellowship, Dr. XXXX' work took very different directions. He utilized single- and sequential-mixing stopped-flow fluorescence spectroscopy as a way to characterize anesthetic actions on the conformational states of the nicotinic acetylcholine receptor. He then used electrophysiological techniques to study another ligand-gated ion channel, the $5HT_3$ receptor. This unique line of research allowed Dr. XXXX to acquire independent grant support for his own trainees, Drs. Ruesch and Solt, and it is currently the basis for his contribution to the MGH program project grant. Most recently, Dr. XXXX' clinical background convinced him of the need for a better, safer general anesthetic, and during the last six years he has carried out cutting-edge research on anesthetic structure-activity relationships. He is now an international leader in the field of new anesthetic development. The anesthetic agents developed in his laboratory at the MGH have been spotlighted in anesthesiology and drug development textbooks, featured in multiple professional journals and in the press, highlighted at annual meetings of the American Society of Anesthesiology, the International Society of Anesthetic Pharmacology, and the Society for Technology in Anesthesia. They have been the subject of numerous editorials and press releases by the MGH and the American Society of Anesthesiologists. Recently, his work was featured on the cover of *Chemical and Engineering News* along with an article describing his important drug development research. A recent review in *Current Pharmaceutical Design* written by a European drug development expert was entirely devoted to Dr. XXXX' investigations, and the author rightfully called his work "exceptionally innovative". The many technologies that arose directly from his investigations have led to four patent applications that form the basis of the start-up company that was mentioned previously.

Annovation BioPharma, Inc. is supported by external venture capital as well as a large pharmaceutical company acting as a co-investor and strategic partner. Partners Healthcare, through its Partners Innovation Fund, has recognized the immense value of this work and has invested alongside of industry. To give some context for this remarkable accomplishment, only 28 other start-ups have been established in all of North America and the United Kingdom and received such funding during 2012. It is particularly impressive that Dr. XXXX has made these very important and highly innovative contributions while continuing his clinical activities, providing superb care to patients and educating anesthesia residents and students in the operating room.

The need for safer anesthetics is urgent. Our surgical population is becoming increasingly elderly and ill, and there are truly no good anesthetic choices for these patients. Developing safe anesthetics is a very difficult goal to achieve, as evidenced by the dearth of new anesthetic agents introduced into clinical practice over the last several decades. Dr. XXXX selected etomidate as his template for making better anesthetics. Etomidate is an intravenous hypnotic that is widely used in the elderly and critically ill for the induction of general anesthesia because, unlike other general anesthetics, it does not produce cardiovascular or respiratory depression and therefore has a high therapeutic index. Unfortunately, its applications are limited, because it binds with very high affinity to the adrenocortical enzyme 11β-hydroxylase, and this dramatically suppresses the synthesis of adrenal steroids. In the early 1980's, the use of continuous infusions of etomidate for sedation of ICU patients caused many deaths from adrenal insufficiency, and this led to the abandonment of etomidate administration by infusion. Since we lack better choices, etomidate is still used in single doses for induction of anesthesia, but concerns remain even here. An intravenous bolus produces only a few minutes of anesthesia, but it results in adrenocortical suppression that can persist for days. Dr. XXXX' knowledge of chemistry and biology, led him to devise two novel strategies that would finally solve this 30 year old problem while preserving etomidate's significant advantages.

The first strategy was to "design out" etomidate's affinity for 11β-hydroxylase. Dr. XXXX deduced that etomidate must bind with high affinity to this CYP450 enzyme because the basic nitrogen in its imidazole ring forms a coordination bond with the heme iron at the enzyme's active site. He recognized that removing this one nitrogen atom would dramatically reduce the binding affinity for 11β-hydroxylase, so he created an etomidate analogue lacking this nitrogen. This new drug (carboetomidate) was several orders of magnitude less potent *in vitro* as an inhibitor of steroid synthesis. More importantly, at anesthetic doses it produced no adrenocortical suppression in vivo (CV ref #49), yet it retained etomidate's excellent safety profile. Dr. XXXX then used an animal model of sepsis to show that unlike etomidate, carboetomidate neither suppresses the pituitary-adrenocortical response nor enhances the production of pro-inflammatory cytokines. These findings may be of great importance for the care of patients with sepsis (CV ref #53). The significance of Dr. XXXX' work was highlighted in an accompanying editorial in *Critical Care Medicine* that called his investigations "ingenious" and the potential implications "profound." This research also led the MGH to file a patent application.

The second strategy was to design an etomidate analogue that would be rapidly metabolized. Dr. XXXX postulated that if etomidate were rapidly cleared, then the adrenocortical suppression

would likely also resolve quickly. Although this "soft analogue" strategy had been used to make other drugs (e.g., esmolol, remifentanil), it had never been used to produce a general anesthetic. Nevertheless, Dr. XXXX carried out the painstaking medicinal chemistry needed to accomplish the task and succeeded in producing the first soft analogue of a general anesthetic (CV ref. #47, 51, 54, 55, 56). Additional modifications improved the anesthetic potency and increased the metabolic clearance (CV ref. #58, 59). The resulting new class of anesthetics includes members that possess all of etomidate's favorable properties, but do not cause persistent adrenocortical suppression. One member of this class is an anesthetic agent with a recovery that is remarkably short (~4 minutes) regardless of the dose or duration of administration. Such a rapid, dose-independent recovery is exhibited by no other general anesthetic and represents an important breakthrough in anesthetic pharmacology. This elegant and exciting work formed the basis of three more patent applications and was the subject of multiple editorials as well as commentaries in textbooks and reviews. Drug development research such as this is normally carried out by medicinal chemists in large industrial settings, and it is exceedingly rare in academic medicine. Dr. XXXX' multiple successes are a testament to his creativity and determination. The results of his work will have an impact well beyond anesthesia, because many imidazole-based drugs produce their therapeutic effects or cause important toxic interactions when they bind to CYP450 enzymes. He has also given us valuable insight into the creation of drugs that are rapidly metabolized. His work will thus serve as a blueprint for the rational design of new drugs in other medical fields.

Apart from his work on drug development, Dr. XXXX' knowledge of chemistry and biophysics has allowed him to conduct innovative research on the molecular mechanisms of anesthetic action:

- He has helped to develop novel anesthetic compounds such as photosensitive analogues of etomidate (CV ref # 37, 50), propofol (CV ref # 52, 61), and barbiturates (CV ref # 60) that may be used as probes to locate and characterize the molecular sites where anesthetics act.
- He has utilized spectroscopic and electrophysiological techniques to characterize the ways in which ligand-gated ion channels work and how their function may be altered by general anesthetics. He was the first to show that the commonly used general anesthetic, isoflurane, potentiates the apparent agonist affinity of the nicotinic acetylcholine receptor (CV ref #10). This work was published in *Anesthesiology* and accompanied by an editorial. He developed a rapid sequential mixing, stopped-flow fluorescence spectroscopic method to detect and characterize the binding and unbinding of a fluorescent agonist to nicotinic acetylcholine receptors. Using this technique, he identified three classes of agonist binding sites on the acetylcholine receptor that were distinguishable by both binding affinities and by the relationship of binding to agonist exposure time. He established that the low and high affinity agonist binding sites belonged to resting and desensitized receptors, respectively. He also quantified, for the first time, the affinity of agonists for the resting state and the rates of binding and unbinding from this conformational state. He also discovered a transient, very-low affinity agonist site on the acetylcholine receptor's open state that is involved in agonist self-inhibition (CV ref #15).

- In addition to his work on the nicotinic receptor, Dr. XXXX has made important contributions to our understanding of another ligand-gated ion channel, the serotonin (5-HT_3) receptor. His seminal work in this area utilized an allosteric kinetic model to give an accurate description of the processes of agonist binding, activation, deactivation, and desensitization in this receptor (CV ref #43). He also defined the multiple actions of general anesthetics on the 5-HT_3 receptor, revealed the subunit-dependence of these actions, and thereby defined an underlying mechanism by which anesthetics act (CV ref #30, 31, 32, 39, 41).
- Understanding the molecular forces that promote anesthetic binding to protein targets has been critical to Dr. XXXX' goal of designing better anesthetic agents. His studies provided the strongest evidence to date that electrostatic interactions are critical determinants of anesthetic binding to relevant proteins. He accomplished this by demonstrating that the pi electron clouds of volatile aromatic compounds may engage in attractive electrostatic interactions with cationic atomic charges on NMDA receptors (CV ref #29). This work was highlighted on the cover of the *Journal of Pharmacology and Experimental Therapeutics*. He further showed that such electrostatic interactions are receptor-selective (CV ref #35, 42, 46). He found an inverse correlation between the potencies of volatile (inhaled) anesthetics to inhibit NMDA vs. $GABA_A$ receptors. This suggests that the combined effects of inhaled anesthetics on these two receptors could account for their *in vivo* anesthetic potencies.

Funding

Dr. XXXX has been the PI (or Project leader) on eight extramural research grants, providing uninterrupted funding for his work on anesthetic pharmacology and anesthetic drug development since he was a research fellow in 1992. It is remarkable that his research funding is accelerating despite dismal recent funding levels at the NIH. He is the PI on an R01 grant focused on the development of novel etomidate analogues. He is also the PI on an R21 grant that proposes to evaluate one etomidate analogue in a model of sepsis. Finally, he is a co-investigator on a program project grant that seeks to define anesthetic sites and mechanisms of action on ligand-gated ion channels. The details of these peer-reviewed grants and previous ones can be reviewed in his curriculum vitae.

Reputation

Dr. XXXX has been invited to give more than 40 national and international talks and plenary lectures (half in the last five years) at major conferences and academic institutions. These include the International Conference of Molecular and Basic Mechanisms of Anesthesia, the Association of University Anesthesiologists, the American Society of Anesthesiologists, the International Society of Anesthetic Pharmacology, the Imperial College in London, the University of Vienna, Johns Hopkins University, the University of Pennsylvania, University of California San Francisco, Washington University in St. Louis, and Vanderbilt University. He has also lectured at the US Environmental Protection Agency and provided them with feedback on their own toxicological work.

Dr. XXXX has served on two ad hoc program project grant review committees for the National Institutes of Health and another review committee for the Royal College of Anaesthetists Project Grants Committee (UK). He is a member of the Board of Directors of the International Society of Anesthetic Pharmacology and serves on the Scientific Advisory Board of the Association of University Anesthesiologists. He has been a consultant and Advisory Board member for the Program Project Grant on Anesthetic Mechanisms based at the University of California San Francisco. He is on the Editorial Boards of ISRN Anesthesiology, F1000 Research, and Dataset Papers in Medicine, an elected member of the Association of University Anesthesiologists, and a member of the Faculty of 1000 in Medicine. He is the Section Editor for General Pharmacology and Pharmacokinetics for BMC Anesthesiology. He has served on multiple committees of the American Society of Anesthesiologists including its highly important and prestigious Committee on Academic Anesthesiology. This committee is the principle provider of input and direction to the American Society of Anesthesiologists on academic medicine. Dr. XXXX has also been a reviewer for more than 20 medical and scientific journals.

Demonstration of scholarship

As we have outlined, Dr. XXXX has a broad and innovative research program focused on understanding how anesthetics work at the molecular and receptor levels, and using that knowledge to develop new anesthetic agents that act more specifically and with fewer side effects. He has published many original, comprehensive, peer-reviewed publications in high impact journals in those areas. The leadership role that he played in these investigations and the critical nature of his contributions are reflected in the fact that on 75% of his original research articles he was either first or senior author and corresponding author. He has authored thirteen reviews, book chapters, and editorials, and co-edited the textbook "*Neural Mechanisms of Anesthesia*". Dr. XXXX has been an invited speaker at numerous national and international conferences and institutions. These include the International Conference on Basic and Systemic Mechanisms of Anesthesia (Canada, Germany, and Japan), the American Society of Anesthesiology, the Association of University Anesthesiologists, and the Environmental Protection Agency. He gives a lecture each year at the MIT Sloane School of Management, where he instructs graduate students on the perioperative management of surgical patients and teaches them about the many novel technologies being developed in his laboratory. He also serves as a guide for these students in the operating room.

EVALUATION FOR TEACHING AND EDUCATION

Over the years, Dr. XXXX has formally advised and mentored more than twenty undergraduate students, post-doctoral research fellows, anesthesiology residents, and staff. Many of these individuals have published with Dr. XXXX and gone on to successful careers in science and medicine. For example, Dr. Ken Solt, MD (Assistant Professor of Anesthesia, HMS) published 13 original peer-reviewed manuscripts, a book chapter, and other publications with Dr. XXXX after completing his MGH residency. Dr. XXXX served as Dr. Solt's mentor on his first research grant, awarded by the Foundation of Anesthesia Education and Research. Dr. Solt has now established his own laboratory and has received K0-8 and R01 grants from the NIH. Dr. Joseph Cotten, MD, PhD (Assistant Professor of Anesthesia, HMS) was similarly mentored by Dr.

XXXX soon after arriving at the MGH from UCSF. Together, they have published 10 peer-reviewed manuscripts and Dr. Cotten has gone on to receive a K0-8 grant from the NIH and establish his own research program. Dr. Warren Sandberg, MD, PhD (Professor and Chair of Anesthesiology, Vanderbilt University) published 1 original peer-reviewed manuscript and 2 book chapters. Dr. XXXX has also had a great impact on the lives of students who are at relatively early stages of their careers. Many come to work in his laboratory as part of their college coursework or immediately after graduating from college. Some investigators don't take the time to mentor individuals who are so inexperienced, but Dr. XXXX is glad to foster their careers. Because of his efforts, many of these students have chosen careers in science and gone on to get MDs or PhDs, including Robert Claycomb (MD, PhD), Katie McClure (MD), Santiago Korten (MD), Elizabeth Kelly (MD), and Renna Stevens (PhD),

As an attending physician in the MGH operating rooms, Dr. XXXX annually teaches over 50 MGH residents, fellows, and medical students from Harvard Medical School and provides airway management instruction to CMTs and clinical fellows from other departments. Dr. XXXX also intensively tutors new residents during their first weeks of residency. His resident lecture on Anesthetic Delivery, Uptake, and Distribution is highly rated because it is so clearly delivered, provides understandable examples, and stimulates provocative discussions. Within the Harvard community, Dr. XXXX has lectured at the annual Harvard Review Course, taught in the Pharmacology and Clinical Therapeutics course (HST), and administered the Objective Structured Competency Exam at HMS.

Part of Dr. XXXX' role as the Director of the DACCPM's Technology Development and Commercialization Initiative, is to oversee an educational program for residents and staff. This novel program, which he developed, provides practical information on a wide range of topics related to technology development and includes lectures relating to intellectual property protection, funding opportunities, start-up company formation, and employment and consulting agreements. He also chairs the DACCPM's Innovation Grants Committee, which oversees funding for technology development within the department.

SIGNIFICANT SUPPORTING ACTIVITIES

Clinical Expertise

Dr. XXXX is a superb clinician who regularly provides anesthesia in the MGH operating rooms during the day and while on call at night. He is highly respected by his colleagues as evidenced by the fact that departmental and division chiefs and other MGH physicians and nurses often ask for Dr. XXXX when they need anesthesia care for themselves or members of their families. He has been repeatedly elected as a Best Doctor in America and appeared in Boston Magazine's list of the best doctors in Boston. These are truly exceptional accomplishments for an individual whose main focus is Investigation. He commonly cares for our sickest surgical patients. He served as a member of the liver transplant team for 17 years. Membership on this team is limited to clinicians with the highest skill and requires special certification because the patients are critically ill and the surgeries complex. He has also lectured on the care of liver transplant patients on multiple occasions as a visiting professor, authored chapters on liver surgery and

transplantation in one of our specialty's most important clinical textbooks, written case reports that have led to important changes in clinical practice, and served as a reviewer for the transplantation field's most prestigious journal. When the Partners Healthcare Network assembled a multi-disciplinary team to redesign care for cancer patients needing surgery and to establish clinical guidelines, Dr. XXXX was asked to represent the anesthesia department. For these efforts, he was awarded one of his three *Partners in Excellence* Awards.

As recognition for his clinical expertise and leadership skills, Dr. XXXX was appointed Vice Chairman for Clinical Administration and Finance for the DACCPM in 2002. As the department's sole Vice Chairman, he had wide ranging responsibilities including management of all clinical activities in the operating rooms at the MGH and affiliated hospitals, overseeing departmental finances, recruiting staff, establishing compensation, and participating (and often leading) more than a dozen departmental and hospital committees. All of these activities made important contributions to the strength and success of the DACCPM.

REVIEW OF SOLICITED LETTERS (in the case of candidates for appointment to the rank of professor, this section to be added after the letters of evaluations are solicited by the Dean's office and shared with the Department Head).

Please provide a brief overview of the letters. Please comment on any concerns raised in the evaluation letters. Note any letters which were solicited but to which no response was received.

STATEMENT OF INTEGRITY

Dr. XXXX is a faculty member in good standing with an appropriate hospital appointment and associated credentialing. To the best of our knowledge, other than as may be indicated in this letter, Dr. XXXX has not been sanctioned or disciplined by a hospital, state licensing board, the NIH, the FDA, or any other legal, regulatory, or institutional authority. There are no current investigations or other concerns known to me that raise questions about her integrity, his competence, or the quality of his/her contributions as a faculty member of Harvard Medical School.

SUMMARY

Dr. XXXX' achievements in his area of excellence of Investigation and the significant supporting activity of Clinical Expertise clearly meet the requirements for promotion to Professor of Anaesthesia. He has an exemplary record of contributions to the basic and translational sciences underlying our specialty. He is a clinician and teacher of extraordinary skill who has been a central and contributory staff member of the MGH Department of Anesthesia's research, educational and clinical missions. He is one of the most effective physicians in advancing our goal of providing safer anesthesia through his combined work in the laboratory and the clinic. Dr. XXXX has received uninterrupted extramural research funding for the last two decades, achieved teaching and mentoring excellence both in the research and clinical realms, national and international recognition as a scientist and innovator, and has exceptional clinical expertise in anesthesiology. In short, he is the "triple-threat" that many in academic medicine strive to be, but rarely achieve. We forward this

application to you with our strongest and most enthusiastic support for his promotion and look forward to the outcome of your deliberations.

Sincerely yours,

Carl E. Rosow, MD, PhD, Provost
Professor of Anaesthesia, Harvard Medical School
Chairman, DACCPM Promotions Committee
Department of Anesthesia and Critical Care

Jeanine Wiener-Kronish, M.D.
Henry Isaiah Dorr Professor of Research
and Teaching in Anaesthetics and Anaesthesia